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Deficiency of Actual Bicarbonate as a Risk Factor for Delayed Kidney Transplant Function from a Living -Related Donor

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Abstract **Introduction.** Kidney transplant recipients are patients with the terminal stage of chronic kidney disease having an initially unfavorable metabolic status, such as hypoplastic anemia, uremic endotoxemia, disturbances in water-electrolyte and acid-base balance. A number of epidemiological studies have shown a link between low serum bicarbonate levels and unfavorable renal outcomes and patient mortality. **Aim of research** was to study acid-base balance disorders in 246 recipients of living related kidney transplantation and its link with the development of delayed transplant function, based on which to establish threshold values of the most informative indicators of acid-base balance, the excess of which was associated with the risk of developing this condition. **Material and methods.** The study included 246 recipients of related kidney transplants from a living donor operated at the State Institute "Republican Specialized Scientific-Practical Medical Center of Surgery named after academician V.Vakhidov" from 2010 to 2020. Parameters of pO_2, pCO2, HCO_3, BE, pH, lactate, hemoglobin, and deep oxygen status (p50) were determined in arterial blood taken in a PICO-70 heparinized syringe using an ABL 800 device (Radiometer, USA). **Results.** Estimation of the transplant function by the level of creatinine reduction in blood serum of kidney transplant recipients showed that 24 hours after the surgery, the primary functioning transplant occurred in 190 (77.2%) patients, delayed transplant function was in 51 (20.8%) patients, transplant dysfunction - in 5 (2.0%) patients (in 2 (0.8%) of them - due to acute rejection). It was found that determination of HCO_3 level and creatinine immediately before surgery is informative to predict the risk of delayed transplant function. A decrease of the actual bicarbonate level of less than 19.8 mmol / l, creatinine of more than 927 μmol / l are risk factors for delayed transplant functioning 24 hours after surgery. **Conclusion.** Kidney transplantation recipients - patients with terminal stage of CKD - immediately before surgery have compensated MA (actual bicarbonate increase and BE), an increase of pO2 and p50 which indicates a deficiency in the metabolic component of ABB regulation and hyperoxia. It is informative to determine the level of aHCO3, creatinine immediately before surgery to predict the risk of delayed transplant function. A decrease in the actual bicarbonate of less than 19.8 mmol / l, creatinine of more than 927 μmol /l are risk factors for delayed graft functioning 24 hours after surgery.

Keywords Transplantation, Kidney, Actual bicarbonate, Transplant delayed function

1. Introduction

Kidney transplantation is the most effective renal replacement therapy [1,2]. Cadaveric transplantation is widely used in the United States, Europe, Russia, Belarus. In particular, the proportion of cadaveric kidney transplantation in Russia makes up 6:1 million people, in Spain - 63: 1 million people, in the USA - 47:1 million people [3]. There is a shortage of donor organs despite the steady increase in the number of kidney transplants worldwide. The demand of population for kidney transplantation is 3,000 per 33 million people in the Republic of Uzbekistan. The legislative basis in our country governs the transplantation of a living-related donor. The advantages of live transplantation are as follows: there is no need to wait for a suitable donor, high immunological compatibility, there is no brain death, a sharp reduction in the time of cold graft ischemia, etc. [4], which is noted in the clinical recommendations of KDIGO [5].

The greatest contribution to the development of the terminal stage of chronic kidney disease (CKD) is made by glomerular and tubulo-interstitial kidney diseases, the morbidity rate of which was 407.6 per 100 thousand of the population in 2016 in our country. Today there are more than 11,000 patients with terminal stage of CKD, more than 3,000 patients receive hemodialysis (according to the Republican

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Information-Analytical Center and the Health Institute data) [6]. After the adoption of the Decree of the President of the Republic of Uzbekistan "On measures for improving the efficiency of the providing nephrological and hemodialysis care to the population of the Republic of Uzbekistan" dated by 12.07.2018, the number of closely related kidney transplants increased. More than 90 kidney transplants have been performed at the Republican Specialized Scientific-Practical Medical Center of Surgery named after academician V. Vakhidov since 2018.One of the important aspects of kidney transplantation is the correction of the initial metabolic status of the recipient for the transplant adequate functioning [7].

Kidney transplant recipients - patients with the terminal stage of chronic kidney disease (CKD), having an initially unfavorable metabolic status such as hypoplastic anemia, uremic endotoxemia, disturbances of water-electrolyte, acid-base balance [8]. A complication of terminal stage of the CKD is chronic metabolic acidosis [9]. A direct correlation between a decrease in glomerular filtration rate (GFR) and a decrease in the level of serum actual bicarbonate as CKD progresses has been proved [10,11]. A number of epidemiological studies have shown a link between low bicarbonate levels and unfavorable renal outcomes and patient mortality [12,13]. The frequency of actual bicarbonate less than 22 mmol / l is about 19% (13-58%) in patients with 4-5 stage of CKD [14]. This level of bicarbonate has been determined as the cut off, requiring correction by the recommendation of KDIGO [15]. Metabolic acidosis (MA) is detected in 15-28% of patients after kidney transplantation, being a predictor of poor prognosis of transplant survival, cardiovascular complications and recipient mortality [16,17,18]. A retrospective cohort study involving 2318 kidney transplant recipients (1997-2015) showed that low CO_2 levels 3 months after kidney transplantation (KT) significantly increased the risk of transplant loss and the risk of recipient death, even when GFR was restored [18]. MA at the level of HCO_3<24 mmol / l is detected in 40% of recipients after KT, which significantly increases the risk of cardiovascular disorders (ischemia, arrhythmia, acute coronary syndrome) [16]. MA at the level of HCO_3<20 mmol / l is associated with an increased risk of death from all causes [17].

The clinical significance of MA estimation and monitoring is reported by many authors, emphasizing the particular vulnerability of kidney transplant cells and the contribution of acid-base balance (ABB) disturbances to the development of endothelial dysfunction, hypertension [19], structural and functional changes in the cardiovascular system, an increase in the expression of pro-inflammatory cytokines genes, which worsens the long-term prognosis and increases the risk of KT functioning disturbance [20,21,22]. In particular, MA and bicarbonate deficiency have a direct negative effect on the kidneys, because an increase in the production of ammonium ions by nephrons at MA conditions triggers an alternative pathway for complement activation which causes tubular lesion [23]. Increased endothelin production at MA initiates tubulo-interstitial damage and contributes to a decrease of GFR [11]. Compensatory increase in the synthesis of bicarbonate in the kidneys with the loss of its ability to reabsorb leads to increased calcification in nephrons [24]. MA promotes the deterioration of perfusion at the level of the microvasculature [20], hyperkalemia and an increase in intracellular sodium, a shift of the oxyhemoglobin dissociation curve to the right with a decrease of hemoglobin affinity to oxygen and desaturation, as well as to violations of deep oxygen status [25]. The homeostasis of hydrogen ions is disrupted at MA which contributes to the inactivation of enzymes, disrupts the function of transmembrane ion channels and receptors, and ultimately leads to cells death [26]. First of all, the most vulnerable are CNS and kidney transplant cells. To ensure the initial functioning of the transplant, careful preoperative preparation is necessary to correct metabolic disorders caused by the absence of excretory function of the kidneys, as well as maintaining a stable constancy of the internal environment of the body at all stages of the perioperative period [24]. It is necessary to avoid ischemic-reperfusion, thrombotic, hemodynamic and intracellular metabolic disorders of the transplant. The study of the acid-base state in KT recipients is important, taking into account the high frequency of metabolic acidosis occurrence in KT recipients and its close relationship with vasomotor, hemodynamic disorders and a direct effect on the activity of intracellular enzyme systems. The study of the respiratory and metabolic components of compensation for ABB disorders has a particular interest, because the decision on the appropriateness and extent of corrective measures depends on this. Determination of the cut off threshold of bicarbonate levels, base excess, anion gap in KT recipients is important.

Aim of research was to study acid-base balance disorders in 246 recipients of living related kidney transplantation and its link with delayed transplant function, to establish threshold values of the most informative indicators of acid-base balance (ABB), which was associated with the risk of graft function disturbances.

2. Material and Methods

The study included 246 recipients of related kidney transplants from a living donor, treated at the State Institute "Republican Specialized Scientific-Practical Medical Center of Surgery named after ac.V.Vakhidov" in 2010-2020. Parameters of ABB (pO2, pCO2, HCO_3, BE, pH), lactate, hemoglobin, and deep oxygen status (p50) were determined in arterial blood taken in a PICO-70 heparinized syringe using an ABL 800 device (Radiometer, USA). Serum creatinine and urea concentrations were determined using a Rayto Chemray-240 automatic biochemical analyzer (China), glomerular filtration rate (GFR) was calculated by MDRD, CKD-EPI. Laboratory tests were done at 2 stages of observation: immediately before surgery (before tracheal intubation - stage 1), 24 hours after surgery (stage 2). The transplant was considered to be primarily functioning if the

serum creatinine level decreased by 10% or more during the first day after KT. Delayed graft function was observed at a decrease of serum creatinine level in these terms less than 10% of the initial level. A primary non-functioning transplant (transplant dysfunction) was detected with an increase of serum creatinine levels to 10% or more on the first day, or within 2 months after surgery while maintaining the need for hemodialysis. Statistical data processing was performed using the Medic-Calc software package. Data are presented as mean (M) and its 95% confidence interval (95% of CI). We used the ROC-curve analysis method to predict the diagnostic significance of quantitative signs (HCO_3, BE, pH, lactate, creatinine, p50) when predicting a specific outcome, including the likelihood of this outcome, calculated using the regression model. The optimal separating value of the above mentioned quantitative sign which allows to classify patients according to the degree of risk of outcome and has the best combination of sensitivity and specificity was determined with its help. The quality of the predictive model obtained by this method was estimated based on the area under the ROC-curve (AUC) with standard deviation (SD) and 95% confidence interval (CI) and the level of statistical significance.

3. Results and Discussion

Table 1. Parameters of acid-base balance (ABB) and uremia before kidney transplantation (stage 1)

Parameter	*M*	*95% CI*	*Reference- interval*	*Unit*
StO_2	99	97-99	>98	
pH	7.35	7.33-7.37	7.35-7.45	
pCO_2	35.1	33.4-36.8	35-45	mmHg
pO2	165.2	149.0-181.3	>80	mmHg
HCO_3	20.2	19.4-21.0	22-28	mmol / l
p50	87	77-87	24-28	mmHg
BE	-5.1	-4.2- -5.9	-2...+2	mmol / l
Na+	136.8	135.9-137.6	135-145	mmol / l
K+	4.9	4.6-5.3	3.5-5.0	mmol / l
Ca++	1.00	0.97-1.04	1-1.25	mmol / l
Cl-	106.2	104.9-107.4	95-105	mmol / l
Anion Gap	13,8	12,5-15,6	8-16	mmol / l
Lactate	0,61	0,54-0,66	0,4-1,5	mmol / l
Hb	89,6	83,1-96,1	130-160 (m) 120-140 (w)	g/l
Creatinine	848,6	797,1-900,2	80-115	µmol / l
Urea	25,7	24,0-27,3	2,3-7,9	mmol / l
GFR	6,6	5,9-7,3	>90	ml/min

There were 204 (82.9%) men and 42 (17.1) women from the total number of recipients (n=246). The mean age was 31.4 years (95% CI 29.5-35.6 years); 234 (95.1%) patients underwent program hemodialysis, the duration of which ranged from 1.5 to 58 months, in 167 (67.8%) patients - from 6 to 12 months. All patients, which undergoing programmed hemodialysis (PHD) received a regular PHD session 18-30 hours before surgery. All examined KT recipients had a terminal stage of CKD as evidenced by the level of creatinine, GFR (Tab. 1).

All of recipients had compromised metabolic status, which include anemia (hyporegenerative, normocytic, normochromic); retention of uremic toxins with serum urea level up to 24-27 mmol / l, a tendency to hyperkalemia and hyperchloremia, hypocalcemia. The study of ABB parameters at the first stage of observation before surgery revealed that the average arterial pH was 7.35, which corresponded to the compensation of metabolic acidosis, which was achieved by respiratory alkalosis at a decrease of actual bicarbonate ($aHCO_3$) by 14.2% ($p<0.05$). KT recipients had a base excess because the BE value exceeded the lower threshold of the reference interval by 2.1 times ($p <0.05$), and pCO_2 was at the level of the lower boundary. Hyperoxia was noted at an increase of pO_2 more than 2 times relative to the threshold value of 80 mm Hg ($p <0.05$), in combination with a significant increase of the partial pressure of oxygen at which hemoglobin was 50% saturated with oxygen - p50 up to 87 mmHg ($p <0.05$).

We suppose, that an increase of p50 can indicate a shift in the hemoglobin dissociation curve to the right, which facilitates the release of oxygen to tissues. But high pO_2 and p50 indicate hyperoxia, but note, that oxygen in high concentration is a potential poison, because it is a source of free radicals (reactive oxygen species-ROS). Cells hyperoxia leads to oxidative stress which poses a risk of transplant cells membrane-destructive processes [27].

Analysis of the recipients' state on the 1st day after the surgery showed that in all cases the transplant began to function intraoperatively. The hourly urine output on the first day after surgery was 102.4 ml (95% CI: 68.9-153.2 ml); the average creatinine level was 692.1 µmol / l (95% CI: 641.6-743.1 µmol / l); urea - 21.2 (95% CI: 19.9-22.5 mmol / l). The average index of creatinine decrease, expressed in%, taking into account that the initial level before the surgery was taken as 100%, made up 75.5% (95% CI 68.6-82.7%). It indicates satisfactory graft function on the first day after surgery, because the decrease was more than 17.3%. It confirms once again the fact that the transplant is highly preserved from living donors (97%), compared with the graft from dead donors (83%) [4,5,15].

However, the use of a personalized approach to assessing changes in serum creatinine level in each recipient showed that only 190 (77.2%) patients had a decrease in its level of more than 10% from the initial one. 51 (20.8%) recipients had a decrease serum creatinine of less than 10% from the initial level and 5 (2%) had an increase in creatinine concentration of more than 10% from the initial one, which indicated KT dysfunction. Immunologically mediated acute KT rejection on the first day after surgery was observed in 2 (0.8%) patients. All of our patients received immunosuppressive therapy. On 1-3 days after transplantation we also did not observe acute tubular necrosis, super-acute, T-cell, antibody-mediated, combined rejection and borderline graft changes in 244 from 246

patients. On 1, 2 and 3 days after surgery they had urine and positive dynamics of a decrease in serum creatinine. Having eliminated the immunological causes of KT dysfunction in 99.2% of the recipients on the first day after surgery, as well as the subsequent positive dynamics of the filtration and excretory function of the kidney, we suggested that other factors, including ABB disorders and retention of uremic toxins were the cause of delayed KT function on the first day after surgery.

Thus, an assessment of graft function by the level of creatinine decrease in the blood of KT recipients showed that 24 hours after surgery, a primary functioning graft occurred in 190 (77.2%) patients, delayed graft function was in 51 (20.8%) cases, transplant dysfunction - in 5 (2.0%) patients, from which due to acute rejection - in 2 (0.8%) cases. A correlation analysis of the percentage reduction in creatinine level on the first day after the surgery with ABB parameters showed that there were reliable relationships only for the actual bicarbonate level before surgery ($r = -0.29$, $p < 0.05$), and with the rest of the ABB parameters, correlation links were weak, unreliable ($p > 0.05$). The use of the method of ROC analysis confirmed the validity of this test in predicting delayed graft function, because AUC for $aHCO_3$ was 0.694 ($p = 0.05$), at 95% CI: 0.550-0.848 (Fig. 1).

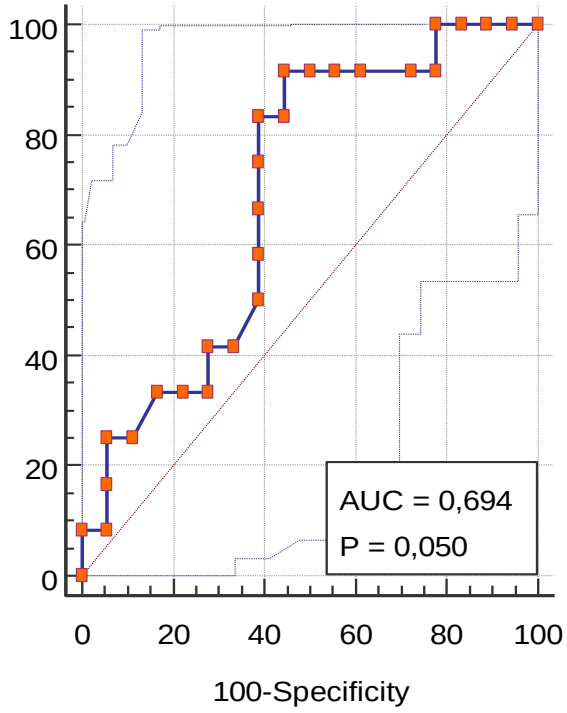

Figure 1. ROC-curve of actual bicarbonate level before transplantation, quality of the test

It was also determined that at an $aHCO_3$ level less than 19.8 mmol / l (sensitivity 91.6%, specificity 55.6%; Youden index J = 0.472), and serum creatinine concentration - more than 927 μmol / l (sensitivity 90.5%, specificity 60.5%; Youden index J = 0.510) there was a risk of delayed graft function (Fig. 2).

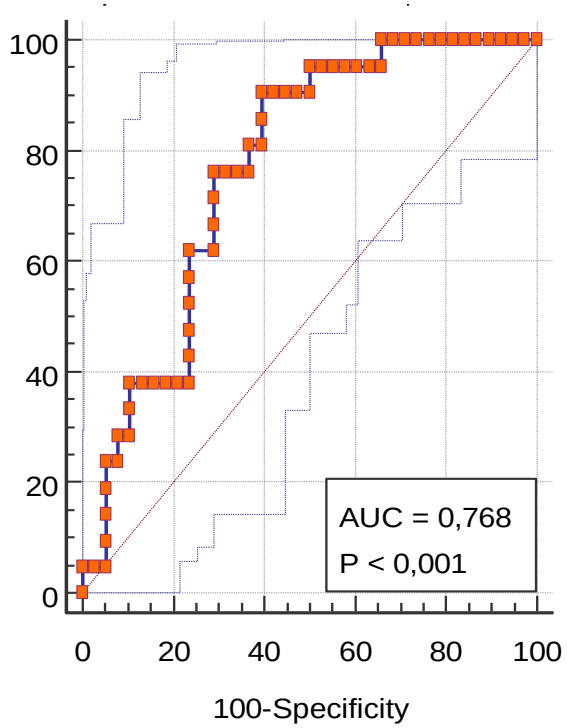

Figure 2. ROC-curve of creatinine level before transplantation, quality of the test

Discussing the results, we note that a high level of creatinine and bicarbonate deficiency, i.e. uremia and compensated metabolic acidosis (MA) in KT recipients may cause a risk of delayed graft function [28]. The mechanism of the adverse effects of MA consists in the fact that under changes of pH the balance of ions of the intercellular and intracellular fluids changes, the internal environment for the functioning of enzymatic systems is violated, additional energy is consumed to restore ion balance, which causes the risk of energy deficiency of transplant cells and, as a result, violation of its functioning [29]. In addition, MA is a perioperative risk factor because it can affects hemodynamic and can cause ischemic reperfusion complications of KT [30]. Vasodilation and a decrease in venous return to the heart occur at a moderate decrease of pH which worsens central hemodynamic [31]. Generalized vessels constriction and tissue hypoperfusion is developed at severe MA (i.e., disorders of intra-organ hemodynamic join), including disturbance in the nutrition of the brain, lungs, and, of course, the transplanted kidney [32]. MA promotes platelet aggregation, increasing thrombogenic potential of blood. Frequently MA is combined with electrolyte disturbances, hyperkalemia, in conditions of which sensitivity to catecholamines is decreased [33]. Also, at MA, the activity of enzymes and the pharmacokinetics of drugs are varied due to the pH shift and changes of biological environment acidity [34]. Possibly, the stability of ABB preoperatively is also important for reperfusion and metabolic disorders of the graft, which may be the reason for its delayed function. It requires further study.

4. Conclusions

Kidney transplantation recipients - patients with terminal stage of CKD - immediately before surgery have compensated MA (actual bicarbonate increase and BE), an increase of pO_2 and p50 which indicates a deficiency in the metabolic component of ABB regulation and hyperoxia.

It is informative to determine the level of $aHCO_3$, creatinine immediately before surgery to predict the risk of delayed transplant function.

A decrease in the actual bicarbonate of less than 19.8 mmol / l, creatinine of more than 927 μmol /l are risk factors for delayed graft functioning 24 hours after surgery.

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